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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,417	08/14/2002	Rainer H Muller	668-59190	8775

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EXAMINER	
EBRAHIM, NABILA G	

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1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/030,417	MULLER, RAINER ET AL.	
	Examiner	Art Unit	
	Nabila G. Ebrahim	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 22-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20, 22-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Applicant's remarks and amendments to the claims dated 5/30/07 is acknowledged.

Status of Claims

Claims 1-20 and 22-47 are pending in the application.

Claims 21 was cancelled.

Status of Office Action: Final.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 7, 10, 11, 13, 15, 22 and 27 remain rejected under 35 USC I02(b) as anticipated by Muller et al US 5, 858, 410 (Muller).

Muller teaches a method for preparing nanoparticles of drugs e.g., corticoids such as prednisolone (col. 22, lines 40-45), the drug particles having average size of 10-1,000 nanometers made by dispersing solid therapeutically active drugs in a solvent and subjecting the dispersion to high-pressure homogenization in a piston-gap homogenizer (abstract and col. 20, lines 23-30) at room temperature (i.e. under 90 degrees; col. 20, lines 35-40).

Claims 1-4, 7, 10, 11, 13, 15, 22 and 27 are anticipated by Muller's '410.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-20 and 22-47 remain rejected under 35 U.S.C.103(a) as being unpatentable over Desai et al WO 98/14174 in (Desai) view of Chen et al. US 5104674 (Chen).

Desai et al (Patent WO '174) discloses a process for preparation of microparticles or nanoparticles of water insoluble drugs; e.g. paclitaxel, an agent that is insoluble in water. The drug is dissolved in an organic solvent (page 17, lines I 5-25), a protein such as albumin is added to stabilize the nanoparticles (page 17, lines 31-34) and the mixture is homogenized under high-pressure homogenization (page 18, lines 6-15 and page 51, lines 25). In disclosing a method for making a pharmaceutically acceptable formulation, Desai discusses sterile-filtration and how drug of particle size less than 200 nm is obtained (page 19, lines 1-16, page 10, lines 24 and page 20, and lines 30-35). According to Desai, the drug particles can be in crystalline or amorphous for (page 13, lines 5-10); details of how to make drug particles of size less than 200 nm are provided. Furthermore, Desai et al also disclose the effect the solvent used has on drug particle size (page 38, lines 5-20) and further discuss the advantage of making the composition in the form of albumin-paclitaxel combination-low toxicity.

one of ordinary skill in the art would be motivated to make paclitaxel or itraconazole compositions according to the methods disclosed in the cited prior art wherein the methods have been shown to provide advantages of reduced volumes and low toxicity products. One of

ordinary skills would expect to obtain economic advantage of making stable aqueous suspensions of water-insoluble drug such as paclitaxel in ready-to-use formulation while maintaining low toxicity of the drug in humans. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.
Desai did not disclose the piston-gap homogenizer required in claims 44-47.

Chen discloses provision of aqueous dispersions of insolubilized microfragmented polysaccharide/protein complexes dispersions. Chen teaches an anhydrous dextrose or dried corn syrup (col. 41, lines 36-45). He also teaches a mixture is cold homogenized using a single-piston homogenizer (example 15)
Accordingly, it would have been obvious to one skilled in the art at the time the invention was made to use a piston homogenizer which provides conditions of intense shear, to fragment the solid complex particles (col. 6, lines 59, and 60).

Response to Arguments

2. Applicant's arguments filed 9/20/06 have been fully considered but they are not persuasive.

Rejection under U.S.C §102 (b)

Applicant argues that:

Muller's abstract describes only the solubility properties of the carrier disclosed in Muller 410. According to the wording the carrier (or active ingredient, respectively) is "insoluble ..... in water, aqueous media and/or organic solvents" and "when introduced" into these media (i.e. the processed or finalized carrier is subsequently introduced into same) the carrier has special properties (e.g. increased saturation solubility).

To respond: Muller's disclosure is clear since it includes the solubility of the drug in organic solvents, consequently, Muller does not exclude organic solvents in the

disclosure. For example, instant claim 13 recites glycerol as a dispersing medium, while Muller uses glycerol in example 4.

Applicant argues that:

When one introduces a compound into a solvent, -as the word solvent says- the compound would dissolve, and not be in the form of small particles any more. Thus the process of claim 38 of Muller as it is worded will not yield in nanosized particulate carrier particles.

In response to this argument, in claim 38, Muller recites a drug that is insoluble, only sparingly soluble or moderately soluble in water, aqueous media and/or organic solvents. The disclosure is clear in the sense of forming dispersion when the particles are added to water or solvent (a solvent is a medium where a solute should dissolve). In addition, the applicant contends that the active compound dispersed in a solvent to high pressure homogenization, the compound would dissolve and not be in the form of small particles any more is not acceptable because as known in science a dispersion is a mixture in which fine particles of one substance are scattered throughout another substance and a dispersion is classed as suspension, colloid or solution. Generally, the particles in a solution are of molecular or ionic size; those in a colloid are larger but too small to be observed with an ordinary microscope; those in a suspension can be observed under a microscope or with the naked eye. A coarse mixture (e.g., sand mixed with sugar) is usually not thought of as dispersion. Please see: (Brown, Theodore. LeMay, Eugen. Bursten, Bruce. Chemistry, The Central Science. 1994 New Jersey: Prentice-Hall, Inc. pages 476, and 477).

This makes the response explicit as the applicant proceeds that the instant active ingredient is dispersed in a non-solvent, which results in a suspension –(the examiner explains that: a suspension is considered one of the forms of a dispersion)- in general it would lead to the same

result if a sparingly-soluble substance is dispersed in a solvent or if an ingredient is dispersed in a non-solvent, in the two cases the end-result is a dispersion.

Applicant argues that:

Claim 38 of the Muller 410 patent must be read in light of its specification. The Muller 410 patent clearly requires using water as the dispersion medium to cause cavitation, as discussed above. Thus, claim 38 must be interpreted in light of the specification of Muller 410 to require using water as a dispersion medium to provide cavitation.

To respond: water is not excluded from the instant claims, it is noted that the reduced water recitation does not exclude water. Note also that the instant disclosure does not teach the amount of water that should be reduced.

Applicant uses the expression water-reduced, this expression does not exclude water.

Please review the instant specification page 6, the last paragraph that discloses:

> An addition of water which does not impair the stability of active ingredients is also advisable if substances or polymers are dissolved in this water which are not, or not sufficiently, soluble in the anhydrous solvent, but are desirable for the final formulation.

Applicant also argues that:

In the present application, an anhydrous or water-reduced medium is used as the dispersion medium. The present invention solves the problems associated with using water in a piston-gap homogenizer. It has been found that water vapor creates bubbles in a piston-gap homogenizer, which subsequently implodes (i.e. cavitation) to lead to particle diminution. This problem is avoided by the present invention. Since the Muller patent does not disclose using an anhydrous or water-reduced medium in the piston-gap homogenizer as the dispersion medium, Muller cannot anticipate the claim invention. Furthermore, by teaching to use water as the dispersion medium to produce cavitation, the Muller patent teaches in a direction opposite to the claimed invention.

To respond to this argument:

Though Muller uses water and/or organic solvent (abstract), the instant application does not exclude water, please see the instant abstract, which discloses:

> The invention relates to superfine microparticles and nanoparticles and a process for their gentle preparation with exclusion of water or minimization of water and/or exclusion of plasticizers and/or reduced temperature load, in which a matrix material is subjected to a high-pressure homogenization process in an anhydrous or water-poor medium and/or at low temperatures, preferably room temperature (20°C) and in particular below the freezing point of water, which leads to a gentle particle reduction with minimization of the impairment of the chemical stability of the homogenized material.

The use of and/or makes the use of water regularly -without reduction- a possibility. Furthermore, in contrast to Applicant's arguments, the disclosure gives the three factors 1) reduction of water 2) exclusion of plasticizer and 3) the low temperature equal importance and teaches by using and/or that one at least of the three factors should be present (not necessarily minimizing water.)

Rejection under U.S.C. §103

Applicant argues that:

Chen is using water as dispersion medium and obtains particles in the micrometer range. The aqueous phase contains e.g. polysaccharides, no mixtures of water with other water miscible liquids are described. Thus, the combination of Desai and Chen uses water. For this reason alone, the Section 103 rejection should be withdrawn.

To respond: water is not excluded from the instant claims, for example, water may be essential to one invention while present in another invention but not essential, however; water is not excluded in the two inventions.

Applicant argues that:

In Desai, "the drug is dissolved in an organic solvent." See page 3 of the Office Action. In contrast, in the claimed method the matrix material is not dissolved in the anhydrous or water-reduced medium. It remains in solid particle form as dispersion.

To respond: Desai explains the solvent differently, the reference discloses that "The microspheres are then washed with a suitable solvent and stored. Leucuta et al. (International Journal of Pharmaceutics 41:213-217 (1988)) describe the method of preparation of heat denatured microspheres." If as the Applicant claims a solvent is for dissolving, it could not be possible to wash the microspheres with a solvent or it should dissolve and disappear.

Applicant argues that:

Desai teaches the preparation of a nanoemulsion, plus subsequent additional steps to obtain drug particles in the nano-meter range. Disruption of large droplets of a liquid requires "relatively" low forces (compared to disrupting solids) and appears feasible. In contrast to this, solids are much more rigid due to their crystalline and solid character. From the Desai disclosure one would not be motivated to process solid drugs using the same process. For this reason alone, the Section 103 rejection should be withdrawn.

In response, an emulsion is defined as: Any stable mixture of two or more immiscible liquids where one liquid (in the form of fine droplets or globules) is dispersed in the other (APA | MLA | Chicago : **Citing this entry** "emulsion". Academic Press Dictionary of Science and Technology (1992). Retrieved 22 November 2006, from xreferplus. http://www.xreferplus.com/entry/3100566). Since Desai uses compounds that are water- and organic-solvent insoluble like taxol, it is expected that the drug particles are dispersed in one of the two liquids which reads on the instant claims. In addition, the instant application includes the use the surfactants (see page 10.) surfactants are defined as: Any surface-active agent or substance that modifies the nature of surfaces, often reducing the surface tension of water;

surfactants are used as wetting agents, detergents, penetrants, and emulsifiers (APA | MLA | Chicago : **Citing this entry:** surfactant. Academic Press Dictionary of Science and Technology (1992). Retrieved 22 November 2006, from xreferplus. tp://www.xreferplus.com/entry/3165447). The definition shows that surfactants are used as emulsifiers which are used to make emulsions. The instant application also discloses that the dispersing medium can be an oil (see page 8). Accordingly, Desai's reference reads on the instant claims.

Furthermore, the examiner cites pages 4, 6 where Desai states that high shear is used to disperse a dispersing agent containing dissolved or suspended pharmacologically active. He also states that in a high-pressure homogenizer at a pressure in the range of about 3,000 up to 30,000 psi. Optionally, the organic and/or aqueous phases are thereafter removed from the mixture after having been subjected to high shear conditions.

Applicant argues that:

Desai does not disclose homogenizing solid particles and Desai does not address the problems associated with implosion shock waves from water evaporation. Desai homogenizes an emulsion (dispersed liquid in an outer liquid phase), the invention a suspension (i.e. solid dispersed in a liquid outer phase).

To respond to this argument: Examiner agrees that Desai does not disclose homogenizing solid particles, neither does the instant application. The instant claims disclose homogenizing a dispersion comprising solid particles while Desai discloses homogenizing an emulsion comprising the solid particles.

Applicant argues that: the guiding conclusion cannot be drawn because Desai uses a special trick to obtain the small particles. One of ordinary skill in the art knows that the formed emulsion droplets lead to very small particles because they "shrink" due to the evaporation of the solvent in the droplets. To get even smaller particles, Desai adds water soluble solvents such as

ethanol to the organic phase (page 10, lines 25- 27) which easily partitions into the water phase leading to further shrinking of the particles. To respond to this argument: Applicant uses the same ethanol in the instant application (see claim 13 and page 9). Accordingly, Desai still reads on the instant application.

Applicant argues also that:

Claim 1 of Desai describes a completely different process, and different processing steps of dissolving the active in the solvent etc. It is not identical with claim 1 of the present invention.

To respond to this argument:

Applicant is respectfully reminded that the rejection is under U.S.C §103, Applicant would not expect to have any identical claims in the reference compared to the instant application.

Applicant finally argues that:

Chen is using water as dispersion medium and obtains particles in the micrometer range. The aqueous phase contains e.g. polysaccharides, no mixtures of water with other water miscible liquids are described. Thus, the combination of Desai and Chen uses water. Chen is using high speed stirrers, e.g. as said on page 12. The high shear zone should best have a shear rate of at least about 37,000 inverse seconds, with a turbulent energy dissipation rate sufficient to raise the temperature of the suspension at least about 5° C. through viscous dissipation of input energy to heat.

To respond to this argument: Water is not excluded from the instant claims. In addition, Chen used pressure homogenizers to achieve a desired degree of microfragmentation (col. 22, lines 34+) and specifically a single-piston homogenizer (example 15)

Accordingly, one of ordinary skill would expect to obtain economic advantage of making stable aqueous suspensions of water-insoluble drug such as paclitaxel in ready-to-use formulation while maintaining low toxicity of the drug in humans. Therefore the invention as a whole would

have been prima facie obvious to one of ordinary skill at the time the invention was made. The skilled artisan would find it also obvious to use a piston homogenizer which provides conditions of intense shear, to fragment the solid complex particles (col. 6, lines 59, and 60).

Documents included in the arguments are provided in the non-final office action.

Conclusion

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nabila G. Ebrahim whose telephone number is 571-272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nabila Ebrahim
10/1/07

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER